Effects of DL-Tetrahydropalmatine on Motor Activity and the Brain Monoamine Concentration in Rats

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Abstract

Behavioral and biochemical methods were used in this study to investigate the effect of DL-THP on motor activity and the concentration of monoamines in rats. Experimental results indicated that DL-THP significantly decreased the motor activity of rats and showed a dose-response pattern; in addition, it produced rigidity at a higher dosage. DL-THP also enhanced the hypomotility induced by haloperidol, but reduced the hypermotility produced by apomorphine. Furthermore, DL-THP significantly decreased the concentration of norepinephrine (NE), dopamine (DA) in the cortex and brain stem at lower and higher dosages, and the concentration of serotonin (5-HT) in the cortex at higher dosages. DL-THP also increased the concentration of homovanillic acid (HVA) in the cortex and brain stem at lower and higher dosages, and the concentration of 5-hydroxyindole acetic acid (5-HIAA) in the cortex at higher dosages. These results suggest that the hypomotility produced by DL-THP may be due to the increase in the turnover rate of dopamine in the cortex and brain stem at lower and higher dosages, and of serotonin in the cortex at higher dosages. (Chinese J. Physiol. 37: 79-82, 1994)

Key Words: DL-tetrahydropalmatine, locomotion, monoamine concentration.

Introduction

DL-Tetrahydropalmatine(DL-THP), i.e., a main active constituent of Corydalis tuber, belongs to the protoberberine type alkaloids and has been proven to possess a sedative effect (3). The sedative mechanism of DL-THP is a brain monoamine depletor by HPLC-ECD (3). Liu investigated the sedative effect of DL-THP, only detecting the concentration of central monoamines and its metabolites (3). He suggested that DL-THP only for those dosages greater than 60 mg/kg show a sedative effect. However, he did not observe any behavioral changes in rats by behavioral pharmacological methods. Furthermore, based on our preliminary experiment, DL-THP for those dosages less than 10 mg/kg has a sedative effect. This effect is the same as that of Liu. We also found that DL-THP had rigid effect in rats in higher dosages. However, because the sedative and rigid effects of DL-THP have never been previously studied by behavioral methods, the sedative and rigid effects of DL-THP and its action of mechanism are investigated in this study by measuring the motor activity and the concentrations of brain monoamines and its metabolites in rats.

Materials and Methods

Animals

Adult male Sprague-Dawley rats (200-300 g) were used for all of the experiments. Rats were housed (six per cage) with food and water ad libitum, in a colony room maintained at a constant temperature (22-25 °C) on a 12:12 h light/dark cycle (lights on 07.00). After the beginning of the treatment, the animals were housed in a separated cage.

Measurement of Motor Activity

The motor activity of individual rats was measured using the MK-ANIMEX activity meter (Model SE. Muromachi Kikai Co., Japan). The sensitivity and tuning of the instrument was adjusted to 35 μA to enable the joint recording of all kinds of motor behavior, i.e., locomotion, rearing, grooming, sniffing and licking. Activity was recorded for 2 hours, starting 5 mins after inserting the animal into

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the test cage. Each rat was used only once and a total of six rats were used for each treatment.

Drugs

DL-THP was dissolved in distilled water containing 10% phosphoric acid. The drug was injected intraperitoneally 10 mins before testing in a volume of 1 ml/kg. Control animals received an equivalent volume of 0.9% saline.

Haloperidol (HAL, Sigma) was dissolved in 0.1 M lactic acid to a concentration of 1 mg/ml and further diluted with physiological saline. Apomorphine (APO, Sigma) was dissolved in ascorbic acid injection.

The following compounds were given before administration of DL-THP as following: HAL (0.01 mg/kg, i.p.) 30 mins before administration of DL-THP (4), APO (0.5 mg/kg, s.c.) 20 mins before administration of DL-THP (6).

Quantification of Monoamines and Its Metabolites by HPLC

DL-THP was given intraperitoneally in a dosage of 10 mg/kg. The rats were decapitated ten minutes later. The entire brain was removed and separated into the cortex and brain stem. The concentrations of NE, DA, 5-HT and their metabolites (VMA, HVA, 5-HIAA) were measured by high performance liquid chromatography (HPLC) with Electrochemical Detector (2,9). HPLC Model 510 (Waters Associates), Data Model M-746 (Waters Associates) and Electrochemical Detector Model LC-4B (Bioanalytical systems) were used.

Statistical Analysis

Results were analyzed statistically using one-way ANOVA, which was followed by Duncan's multiple range test to make a comparison of their differences. P values less than 0.05 were required for statistical significance.

Results

Effects of DL-THP on Motor Activity

As shown in Fig. 1, DL-THP could produce a significant decrease in motor activity and show a dose-dependent response ($p < 0.05 - 0.001$). However, it produced rigidity at a higher dosage (20 mg/kg, i.p.).

Rats treated with HAL appeared to be behaviorally depressed. The hypomotility produced by HAL was significantly augmented by DL-THP ($p < 0.01$) (Fig. 2).

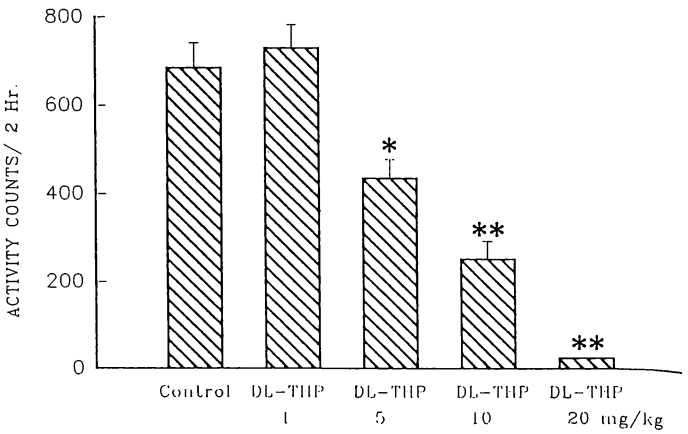

Fig. 1. Effects of DL-tetrahydropalmatine on the motor activity in rats. Value are mean ± SEM of six rats. Statistical comparisons of the DL-THP group vs. the control group use one-way ANOVA for repeated measures followed by Duncan's multiple range test (*$p<0.05$, **$p<0.01$).

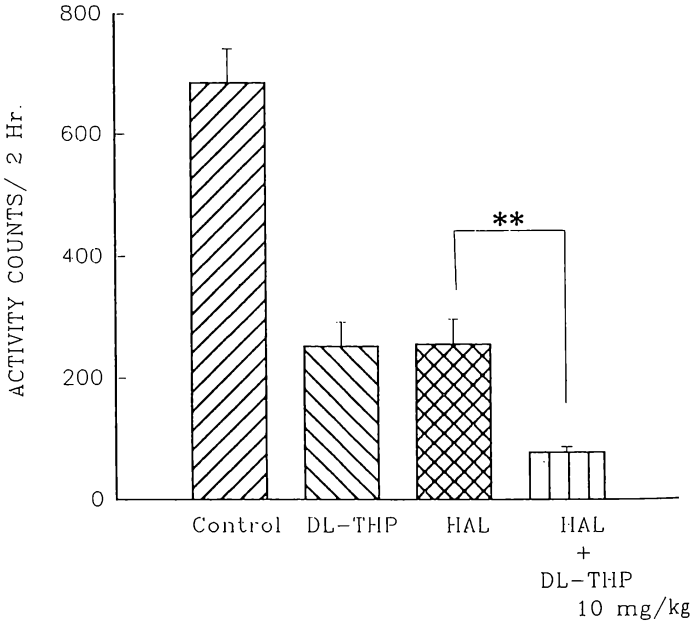

Fig. 2. Effects of DL-tetrahydropalmatine on the motor activity produced by haloperidol in rats. DL-THP, DL-tetrahydropalmatine (10 mg/kg, i.p.), HAL, haloperidol (0.001 mg/kg, i.p.). Values are mean ± SEM of six rats. **$p<0.01$ with respect to HAL group using one-way ANOVA for repeated measures followed by Duncan's multiple range test.

As shown in Fig. 3, APO produced significant hypermotility. The hypermotility produced by APO was significantly reduced by DL-THP ($p<0.01$).

Effects of DL-THP on the Concentrations of Monoamines and Its Metabolites in the Brain Stem and Cerebral Cortex.

As indicated in Table 1, DL-THP (10 mg/kg, i.p.) significantly decreased the levels of NE ($p < 0.01$), DA ($p < 0.05$), and increased the levels of HVA

Table 1. Effects of DL-tetrahydropalmatine (DL-THP) on the concentration of monoamines and its metabolites in cerebral cortex in rats.

Treatment	Cerebral Cortex								
	NE (ng/g)	VMA (ng/g)	VMA/NE	DA (ng/g)	HVA (ng/g)	HVA/DA	5-HT (ng/g)	5-HIAA (ng/g)	5-HIAA/5-HT
0.9% saline	2267 ± 305	325 ± 19	0.143	879 ± 72	143 ± 24	0.163	1940 ± 307	935 ± 17	0.482
DL-THP (10 mg/kg, i.p.)	1363 ± 91**	341 ± 27	0.250	557 ± 56*	216 ± 42*	0.389	1620 ± 172	1049 ± 46	0.648
DL-THP (20 mg/kg, i.p.)	981 ± 80**	380 ± 24	0.387	463 ± 84**	297 ± 34**	0.641	965 ± 78**	1241 ± 42**	1.287

Data presented as the mean ± SEM of 6 rats for each group.
*significantly different from the control value (saline group), *$p < 0.05$, **$p < 0.01$ with respect to the control group using one-way ANOVA for repeated measured followed by Duncan's multiple range test.

Table 2. Effects of DL-tetrahydropalmatine (DL-THP) on the concentration of monoamines and its metabolites in brain stem in rats.

Treatment	Brain Stem								
	NE (ng/g)	VMA (ng/g)	VMA/NE	DA (ng/g)	HVA (ng/g)	HVA/DA	5-HT (ng/g)	5-HIAA (ng/g)	5-HIAA/5-HT
0.9% saline	4389 ± 144	650 ± 12	0.148	2666 ± 373	370 ± 26	0.139	794 ± 60	316 ± 47	0.398
DL-THP (10 mg/kg, i.p.)	2669 ± 116**	560 ± 13	0.210	1031 ± 209*	484 ± 34*	0.469	681 ± 32	338 ± 27	0.496
DL-THP (20 mg/kg, i.p.)	2215 ± 98**	629 ± 13	0.284	700 ± 45**	557 ± 36**	0.796	654 ± 52	380 ± 45	0.581

Data presented as the mean ± SEM of 6 rats for each group.
*significantly different from the control value (saline group), *$p < 0.05$, **$p < 0.01$ with respect to the control group using one-way ANOVA for repeated measures followed by Duncan's multiple range test.

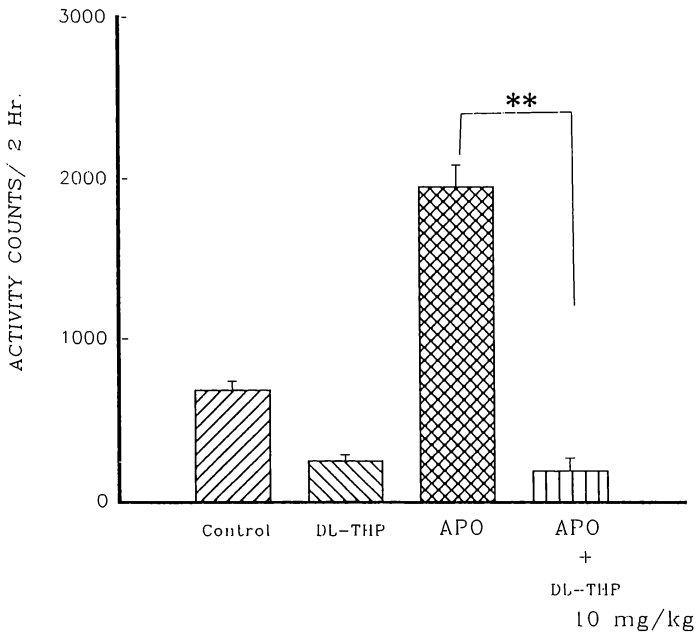

Fig. 3. Effects of DL-tetrahydropalmatine on the motor activity produced by apomorphine in rats. DL-THP, DL-tetrahydropalmatine (10 mg/kg, i.p.); APO, apomorphine (0.5 mg/kg, s.c.). Values are mean ± SEM of six rats. **$p < 0.01$ with respect to APO group using one-way ANOVA for repeated measures followed by Duncan's multiple range test.

($p < 0.05$). Also, DL-THP (20 mg/kg, i.p.) significantly decreased the level of NE, DA and 5-HIAA ($p < 0.01$), and increased the level of HVA ($p < 0.01$) and 5-HIAA ($p < 0.01$) in the cortex.

As revealed in Table 2, DL-THP (10, 20 mg/kg, i.p.) significantly decreased the levels of NE ($p < 0.01$), DA ($p < 0.05$, 0.01), and increased the level of HVA ($p < 0.05$, 0.01) in the brain stem.

Discussion

As indicated from the results in Fig 1, DL-THP significantly decreased the motor activity and shown a dose-response pattern. However, the rats treated with DL-THP at 20 mg/kg produced a rigid syndrome. This result manifested the observation that DL-THP has a sedative effect at those dosages less than 10 mg/kg and a rigid effect at those dosages greater than 20 mg/kg. Therefore, the sedative mechanism and rigid effect of DL-THP were investigated here by measuring the motor activity and concentration of central monoamines and its metabolites.

The relationship between the sedative effect of DL-THP and monoaminergic activity was next in-

vestigated, Some drugs (haloperidol and apomorphine) which have an effect on the central monoaminergic system were used, to produce behavioral changes in rats. Haloperidol (a DA receptor blocker) (5) generally reduces motor activity. Whereas apomorphine (a DA receptor agonist) (6) produces hypermotility. DL-THP significantly augmented the hypomotility produced by haloperidol, and reduced the hypermotility produced by APO. These facts imply that the sedative effect of DL-THP may be involved in the decrease in central dopaminergic activity.

In order to understand the relationship of sedative effect of DL-THP and the levels of brain monoamines and its metabolites, the levels of the central monoamines and its metabolites in rats were detected. These results indicated that DL-THP (10 mg/kg, i.p.) significantly decreased the levels of NE and DA and increased the level of HVA in the cortex and brain stem. Also, DL-THP increased the ratio of VMA/NE, HVA/DA in the cortex and brain stem. Those same results indicated that DL-THP increased the NE and DA turnover rate in the cortex and brain stem. DA is generally assumed to be an excitatory neurotransmitter in the cortex and brain stem (1). Thus, the inhibitory effect of DL-THP on motor activity in rats is apparently related to the decrease of DA levels in the cortex and brain stem.

The behavioral changes of DL-THP were observed by naive behavioral observation, revealing that DL-THP produced a rigid effect at those dosages greater than 20 mg/kg. In order to understand the relationship of the rigid effect of DL-THP and the levels of monoamines and its metabolites, the levels of the central monoamines and its metabolites in rats were also detected. Those results indicated that DL-THP (20 mg/kg, i.p.) significantly decreases the level of NE, DA in the cortex and brain stem and 5-HT in the cortex, as well as increases the level of HVA in the cortex and brain stem and 5-HIAA in the cortex. DL-THP increased the ratio of VMA/NE, HVA/DA in the cortex and brain stem and 5-HIAA/5-HT in the cortex. Those same results further indicated that DL-THP increased the NE and DA turnover rates in the cortex and brain stem, and 5-HT turnover rate in the cortex. The more the activities of brain monoaminergic system decrease would generally imply, the more rigid syndrome would be produced (7,8). These results indicated that the rigid effect of DL-THP at 20 mg/kg dosage may be related to the decrease in central monoaminergic activity in the cortex and dopaminergic activity in the brain stem.

We can conclude that the sedative mechanism of DL-THP at the dosage of 10 mg/kg may be related to the decrease in the central dopaminergic activity. Also, the rigid effect of DL-THP at the dosage of 20 mg/kg may be related to the decrease in the monoaminergic activity in the cortex and the dopaminergic activity in the brain stem.

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